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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,872	11/26/2003	Stephen Dudley Holmes	P50186-2XC3	9326

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EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,872	HOLMES ET AL.	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-18 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-11, 14-18 and 30-38 in the reply filed on 2/8/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC 112

Claims 3 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of 3426A11C1B9, and monoclonal antibodies 6A1 and 3B9. It is not clear that hybridomas possessing the identical properties of the aforementioned cell lines are

known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed hybridoma, a suitable deposit for patent purposes, evidence of public availability of the claimed hybridoma or evidence of the reproducibility without undue experimentation of the claimed hybridoma, is required.

Applicant's referral to the deposit of hybridoma 3426A11C1B9 as disclosed on page 32 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met. Additionally, the hybridoma is for monoclonal antibody 6A1 not 3B9.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature

and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 and 17-18 and 32-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18, 22-25 and 28-29 and 34-35 of US Patent No. 5914110.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the only difference between the two inventions is the scope of the invention. Specifically, the instant set of claims are directed to fusion proteins

having specificity for humans IL-4 wherein the CDRs of the fusion proteins are obtained from neutralizing antibody 3B9 and 6A1 and have CDRs of SEQ ID No. 20, 22, 24, 26, 16, 18, 28 and wherein the heavy and light chain are SEQ ID No. 2 and 4 and the use of these fusion proteins in pharmaceutical compositions to treat allergies and other conditions associated with excess IgE production. The instant set of claims are also directed to neutralizing monoclonal antibodies including 6A1 produced from hybridoma 3426A11C1B9. The fusion proteins of the instant invention are broader in scope than those of the patent because the fusion proteins of the patent are limited to fusion proteins having three CDRs per heavy or light chain and the instant invention only has one (Note that the SEQ ID NO. in both the patent and the application are identical). The monoclonal antibodies of the instant invention are broader in scope than that of the patent because the patent is limited to monoclonal antibodies that bind to the epitope of 6A1 or 3B9 and that claims of the instant invention encompass all neutralizing monoclonal antibodies that bind to IL-4.

Claim Rejections - 35 USC 112

Claims 17-18 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in In Re

Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex Parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the breath of the claims,
5. the amount of direction or guidance present, and
6. the presence or absence of working examples.

The following is an analysis of these factors in relationship to this application.

Nature of the invention

Applicant discloses and claims the use of fusion protein (antibodies) to treat and/or diagnose allergies and other conditions associated with excess IgE production.

State of the Art/ Predictability

The claimed invention pertains to the highly experimental and unpredictable field of in vivo therapy using monoclonal antibodies. Articles by Waldmann and Harris are cited in order to establish the general state of the art and level of predictability of in vivo human therapy using monoclonal antibodies. The cited references establish that numerous experimental and clinical studies have determined that the effective application of antibody-based therapy methods for in vivo treatment of human diseases has been extremely limited. The complexity and unpredictability of the art to which the invention pertains provides reasonable basis to question the accuracy of applicant's assertion that the antibodies can be used for effective therapy in vivo.

Waldmann teaches on page 1657 that, to date, low therapeutic efficacy has been attained in the use of unmodified murine monoclonal antibodies for therapy of human disorders such as cancer and infectious diseases. Harris summarizes recent

conferences (Feb. 1993) in the field of therapeutic monoclonal antibodies and teaches that there is widespread acceptance in the art that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy. Harris cites several problems limiting the effective use of rodent monoclonal antibodies including (1) short in vivo half-life; (2) poor recognition of rodent immunoglobulin constant regions with human effector cells and (3) the human immune response (HAMA) against murine proteins. Anti-murine antibodies elicited in the HAMA response complex with administered antibodies and have the effect of rendering repeated antibody dosing ineffective.

The complexity and unpredictability of the art to which the invention pertains provides reasonable basis to question as to the accuracy of applicant's assertion that the antibodies can be used for effective therapy in vivo.

Guidance/Working Examples

Applicant has provided in vitro assays. Those of skill in the art recognize that in vitro assays are useful to screen the effects of agents on target cells. However, in vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay, does not permit a simple extrapolation of in vitro assays to in vivo therapeutic/diagnostic efficacy with any reasonable degree of predictability. In vitro assays depend on cell culture and therefore do not entirely simulate in vivo conditions. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further, an therapeutic/diagnostic agent must accomplish several tasks to be effective. It must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In the assays, the agent is in contact with cells during the entire exposure

period. This is not the case in vivo, where exposure at the target site may be delayed or inadequate. Thus, the in vitro assays are not correlatable to the treatment or diagnosis of allergies and other conditions associated with excess IgE production.

Breadth of the claims

The specification does not teach how to produce and use functional proteins having binding specifically for IL-4 which have the structural elements defined by claim 1. Claims 1-4 require that the claimed fusion protein be comprised of amino acid sequences from only a single CDR. Claims 7 and 8 define fusion proteins which are comprised only of three amino acid sequences of CDRs. It is noted that claims 1-4 do not specify that the amino acid sequences referred to comprise entire CDR. The claims do not require that any additionally elements are present in the antigen-binding regions of the fusion proteins.

The specification only teaches how to produce fusion proteins which comprise the full complement of CDRs characteristic of a non-human donor antibody which are fused in the order in which they exist in the donor antibody, to the framework of a human acceptor antibody. It is known that the sequences and conformations of immunoglobulin CDRs and framework regions are critical in maintaining the antibody binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and fused to appropriate human framework sequences are required in order to produce a protein having antigen-binding function and the proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the

contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human framework sequence, or no framework sequences, would possess the functional characteristics of binding with high affinity to and neutralizing IL-4. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims.

In view of the above, it is the Examiner's position that one skilled in the art could not make and/or use the invention without undue experimentation.

Claims 1-11 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fusion proteins containing the full complement of CDR's, does not reasonably provide enablement for fusion proteins containing only one CDR or CDR's in an unspecified order. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not teach how to produce and use functional proteins having binding specifically for IL-4 which have the structural elements defined by claim 1. Claims 1-4 require that the claimed fusion protein be comprised of amino acid sequences from only a single CDR. Claims 7 and 8 define fusion proteins which are comprised only of three amino acid sequences of CDRs. It is noted that claims 1-4 do not specify that the amino acid sequences referred to comprise entire CDR. The claims do not require that any additionally elements are present in the antigen-binding regions of the fusion proteins.

The specification only teaches how to produce fusion proteins which comprise the full complement of CDRs characteristic of a non-human donor antibody which are fused in the order in which they exist in the donor antibody, to the framework of a human acceptor antibody. It is known that the sequences and conformations of immunoglobulin CDRs and framework regions are critical in maintaining the antibody binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and fused to appropriate human framework sequences are required in order to produce a protein having antigen-binding function and the proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is well

established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human framework sequence, or no framework sequences, would possess the functional characteristics of binding with high affinity to and neutralizing IL-4. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims.

Claims 1-11 and 14-18 and 30-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In the claims, the terminology "is derived from" renders the claim vauge and indefinite. The manner of derivation referred to is not kown. This phrase is not one which has a single defined meaning in the art nor is it one which is defined in the specification. In the absence of an ascertainable meaning for the phrase, one of skill could not determine the meets and bounds of the claimed subject matter. It is likely that derivation of the subject CDRs would alter the binding characteristics of the resulting fusion protein. Reciting a functional limitation for the CDR in the claim would help overcome this rejection.

b. In the claim, the terminology "neutralizing renders the claim vague and indefinite. "Neutralizing" what? Which activity of IL-4 is neutralized.

c. In claim 1, the terminology "a first fusion partner" render the claim vague and indefinite. As defined in the specification, this terminology is a nucleic acid sequence. Thus, if appears that applicant is claiming a nucleic acid sequence (first fusion partner) attached to a CDR (which is composed of amino acids)? This is a fusion protein as indicated in the first line of the claim.

d. Claim 2 is vague and indefinite because it is not clear how and where the second fusion partner is attached to the fusion protein.

e. Claim 4 is indefinite in the recitation of a fusion protein wherein a CDR is fused to a second fusion partner which comprises all "or part" of a heavy or light chain or both. It is not known which particular part of the heavy or light chain is referred to. If the portion referred to is a region of the heavy and/or light chain, the characteristics of the constant regions comprising the fusion protein will alter the physical and biological characteristics of the molecule. If the portion referred to is a variable region sequence, the characteristics of the region comprising the fusion protein will affect binding characteristics.

f. Claims 5 and 6 are vague and indefinite because it is not clear what and how the recited sequences are linked or even if they are linked.

g. In claims 5-6, there is no antecedent basis for "said fusion partner sequence".

h. In claims 7-9 there is no antecedent basis for "said amino acid sequence".

i. In claim 8, the first amino acid in SEQ ID NO. 16 should be lys not leu (see sequence listing.

j. In claims 7-11, it is unclear if each amino acid sequence are the CDR of part of the CDR. It is also unclear if each sequence can be present three times to give the full complement of CDRs or each only present once?

k. Claims 30-32 are indefinite in the recitation of "high titer". The phrase does not have a defined meaning in the art and thus one skilled in the at could be determine the meets and bounds of the claims.

l. In claims 37-38, it is unclear as to what applicant means by "identifying characteristics". What characteristics?

m. In claim 31 it is unclear what applicant means by "aldehyde-coupled" IL-4. Where is the aldehyde coupled?

n. in claim 31, line 1 "ahigh" should be --a high--.

Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-9, 11 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 93/04173(3/4/93).

The reference discloses the sequence of Mae15 light chain as containing the sequence AASNLES (corresponds to SEQ ID No. 18 of the instant application)(see fig. 2). Mae15 is made by recombinant techniques therefore exists in a fusion protein (p. 34-35 and 39). The antibody is used in assays which inherently use a pharmaceutically acceptable formulation. It is inherent that Mae15 has the ability to neutralize IL-4 with the claimed dissociation constant.

Claims 1-2, 4, 14-17, 31-34 and 36 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 93/17106(9/2/93).

This reference discloses recombinant methods (using fusion proteins) of making humanized antibodies from rat antibody that have the ability to neutralize human IL-4 activity (abstract and pages 41-57). The reference discloses humanizing the heavy and/or light chains and methods of screening the antibodies for IL-4 activity.

Claims 1-2, 4, 8-9, 11 and 14 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 327000.

This reference discloses making humanized antibodies (reference calls them chimeric antibodies) wherein the amino acid sequence of the light chain contains the sequence lys-ala-ser-gln-ser-val-asp-tyr-asp-gly-asp-ser-tyr-met-asn (corresponds to SEQ ID No. 16 of the instant application (p. 4, lines 39). This light chain is made as part of a fusion protein (p. 5 and examples). The antibody is used in assays which inherently use a pharmaceutically acceptable formulation. It is inherent that humanized antibodies have the ability to neutralize IL-4 with the claimed dissociation constant.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Weigert et al Nature vol. 276 p. 785 (1978).

This reference discloses the amino acid sequence of light chains as comprising amino acid sequences comprising Seq Id NO. 16 and 18 of the instant invention (see figure 2).

Claims 1-2, 4 and 7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Perfetti et al Mole. Immunol. vol. 287 p. 505 (1991).

This reference discloses the amino acid sequence of the heavy chain as containing thr-ser-gly-met-gly-val-ser (corresponds to SEQ.. ID No. 22 of the instant application (fig. 3) and the production of said heavy chain using recombinant technology.

Claims 32-34 are rejected under 35 U.S.C. 102(b) as anticipated by Ramanathan et al WO 91/09059.

Ramanathan et al teach mouse mab produced by immunization with a peptide corresponding to residues 61-82 of human IL-4 (see page 26). The ability to neutralize IL-4 is deemed to be an inherent characteristic of the referenced antibodies in view of the showing that pab elicited against the same peptide immunogen blocked binding of human IL-4 to its receptor. A dissociation constant of less than 2×10^{-10} M is deemed to be an inherent characteristic of the referenced antibodies given that most mab have affinity constants of 2×10^{-10} M or less.

Claims 30 and 32-34 are rejected under 35 U.S.C. 102(b) as anticipated by JP-327725.

JP-327725 (Derwent Publ. Ltd. abstract 91-284372) teaches high affinity mouse monoclonal antibodies specific for human IL-4 which neutralize IL-4 activity and a

method for detection of IL-4 comprising the steps of contacting a biological fluid with monoclonal antibody and assaying for the occurrence of binding of antibody and IL-4 (see sections 3 and 11).

Claims 32-33 and 36 are rejected under 35 U.S.C. 102(b) as anticipated by Chreiten et al J. Immunol. Methods vol. 117 p. 67 (1991).

Cretien et al tech that rat mab 11B4 which inhibits the TCGF bioactivity of human IL-4 (see page 76). A dissociation constant of less than 1 x 10^{-10} M is deemed to be an inherent characteristic of the referenced antibody given that most mab have affinity constants of 1 x 10^{-10} M or less.

Claim Rejections - 35 USC 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> or (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 32-34 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ramanathan et al WO 91/09059 or JP-327725.

Ramanathan et al teach mouse mab produced by immunization with a peptide corresponding to residues 61-82 of human IL-4 (see page 26). The ability to neutralize

IL-4 is deemed to be an inherent characteristic of the referenced antibodies in view of the showing that pab elicited against the same peptide immunogen blocked binding of human IL-4 to its receptor. A dissociation constant of less than 2×10^{-10} M is deemed to be an inherent characteristic of the referenced antibodies given that most mab have affinity constants of 2×10^{-10} M or less.

JP-327725 (Derwent Publ. Ltd. abstract 91-284372) teaches high affinity mouse monoclonal antibodies specific for human IL-4 which neutralize IL-4 activity and a method for detection of IL-4 comprising the steps of contacting a biological fluid with monoclonal antibody and assaying for the occurrence of binding of antibody and IL-4 (see sections 3 and 11).

The invention of claim 1 is characterized as a fusion protein. However, given the lack of specified structural elements in the claims to distinguish the claimed fusion proteins from those that would be produced by hybridoma as disclosed in the cited references, the claimed fusion protein is deemed to be the same as the monoclonal antibodies taught in the prior art.

Although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claim process. However, the purification of a product by a particular process does not impart novelty to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPA 964 (CAFC 1985); In re Marosi, 218 USPO 289, 292-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972).

Therefore, even if a particular process used to prepare a product in novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPO 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599,601, 38 USPO 143-145 (CCPA 1938); In re Bergv, 563 F. 2d 1031, 1035,195 USPO 344, 348 (CCPA 1977) vacated 438 US 902 91978); and United States v. Ciba-Geigy Corp. 508 F. Supp. 1157, 1171, 211 USPO 529, 543 (DNJ 1979).

Even if the prior art antibodies are not identical to those instantly claimed, given the teaching of the prior art specifically characterizing the anti-IL-4 antibodies in combination with conventional hybridoma methods it would have been prima facie obvious to produce similar antibodies having the same specificity and function. One of ordinary skill in the art would have expected to obtain antibodies having the claimed affinity, since affinity constants for antigen-antibody binding within the range of 10^5 mol $^{-1}$ to greater than 10^{10} mol $^{-1}$ are commonly observed. It would have been prima facie obvious to apply well established immunoglobulin gene cloning and expression methods to produce fusion proteins such as chimeric antibodies, having variable regions of the antibodies suggested by the prior art.

Claims 1 and 32-33 and 36 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chreiten et al J. Immunol. Methods vol. 117 p. 67 (1991).

Cretien et al tech that rat mab 11B4 which inhibits the TCGF bioactivity of human IL-4 (see page 76). A dissociation constant of less than 1×10^{-10} M is deemed to be an inherent characteristic of the referenced antibody given that most mab have affinity constants of 1×10^{-10} M or less.

The invention of claim 1 is characterized as a fusion protein. However, given the lack of specified structural elements in the claims to distinguish the claimed fusion proteins from those that would be produced by hybridoma as disclosed in the cited references, the claimed fusion protein is deemed to be the same as the monoclonal antibodies taught in the prior art.

Although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claim process. However, the purification of a product by a particular process does not impart novelty to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPA 964 (CAFC 1985); In re Marosi, 218 USPO 289, 292-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972).

Therefore, even if a particular process used to prepare a product in novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPO 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599,601, 38 USPO 143-145 (CCPA 1938); In re Bergy, 563 F. 2d 1031,

1035,195 USPO 344, 348 (CCPA 1977) vacated 438 US 902 91978); and United States v. Ciba-Geigy Corp. 508 F. Supp. 1157, 1171, 211 USPO 529, 543 (DNJ 1979).

Even if the prior art antibodies are not identical to those instantly claimed, given the teaching of the prior art specifically characterizing the anti-IL-4 antibodies in combination with conventional hybridoma methods it would have been prima facie obvious to produce similar antibodies having the same specificity and function. One of ordinary skill in the art would have expected to obtain antibodies having the claimed affinity, since affinity constants for antigen-antibody binding within the range of 10^5 mol $^{-1}$ to greater than 10^{10} mol $^{-1}$ are commonly observed. It would have been prima facie obvious to apply well established immunoglobulin gene cloning and expression methods to produce fusion proteins such as chimeric antibodies, having variable regions of the antibodies suggested by the prior art.

Claim Rejections - 35 USC 103

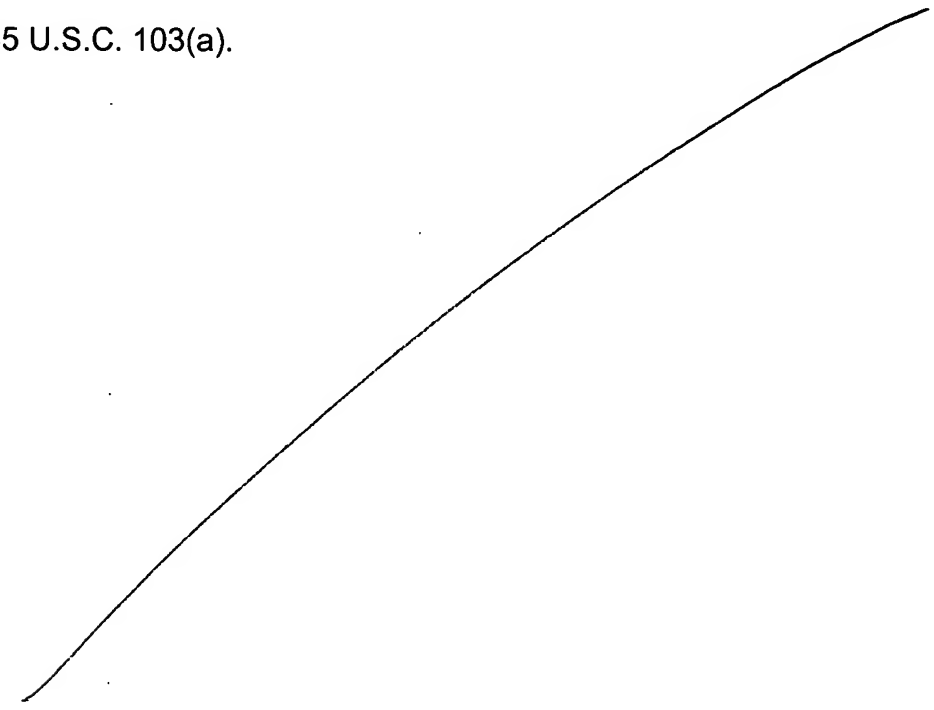
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).



Claims 1-4 and 14-17, 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al WO 90/07861 in view of Co et al Nature vol. 351 p. 501 (1991), Abrams et al US 5041381, Chreiten et al J. Immunol. Methods vol. 117 p. 67 (1991), Curtis et al US 5108910, Orlandi PNAS vol. 86 p. 3833 (1989), JP-327725, Coffman et al WO 89/06975 and Maggio Enzyme-Immunoassay CRC Press Inc. 1980 pp. 167-178.

Queen et al disclose methods for producing fusion proteins which are chimeric or CDR-grafter humanized antibodies. The reference discloses an approach to producing CDR grafter antibodies which involves the selection of human variable regions which are homologous to the murine variable region to be humanized and computer modeling to identify murine framework residues which make key contacts with CDR's, which are then introduced into human frameworks (see abstract, p 4-6 and 10-11). This reference also discloses that the art recognizes that humanized antibodies are expected to have advantages for use in vivo human therapy (page 3).

The only differences between the instant invention and the reference is the specificity of the antibody, the pharmaceutical compositions, the cloning of the immunoglobulin variable domains and the advantages of using a fusion protein linked to an additional peptide.

Co et al disclose that the art recognized that humanized antibodies were expected to have advantages for use in vivo human therapy application (page 501).

Abrams et al disclose rat monoclonal antibody 1C1.11B4.6 which has specificity for human IL-4. The authors suggest that neutralizing anti-IL-4 antibodies have potential therapeutic utility (see col. 2). Abrams further teaches of compositions containing a therapeutic amount of at least one monoclonal antibody in a pharmaceutically effective carrier. (col. 5, lines 55-60).

Curtis et al disclose advantages of an amino acid sequence of the fusion protein being linked to an additional peptide. This peptide is highly antigenic and provides an epitope reversible bound by a specific monoclonal antibody. Curtis concludes that this second fusion to the original protein is superior over the original fusion protein of Granulocyte Marcophage Colony Stimulating Factor and IL-3 alone (col. 7).

Chretien et al teach neutralizing anti-IL-4 rat mab 11B4 which has use in immunoenzymatic assay, immunopurification and potential implications in certain pathological conditions.

JP-327725 (Derwent Publ. Ltd. abstract 91-284372) teaches high affinity mouse monoclonal antibodies specific for human IL-4 which neutralize IL-4 activity and a method for detection of IL-4 comprising the steps of contacting a biological fluid with monoclonal antibody and assaying for the occurrence of binding of antibody and IL-4 (see sections 3 and 11).

Orlandi et al disclose methods using primers for V domains of mouse immunoglobulin heavy and light chains for forced cloning and amplification of mouse hybridomas.

Maggio disclose that high affinity antibodies display affinity constants on the order of 10^{10} $(M/l)^{-1}$ to 10^{12} $(M/l)^{-1}$ resulting in sensitivities of about 10^{10} and 10^{12} M. Maggio further teaches that affinity between antigen and antibody probably limits the sensitivity in immunoassay procedures that use the most sensitive lab-detection methods.

Coffman et al disclose blocking antibodies specific for IL-4 have potential for reducing IgE responses associated with certain human immune disorders.

In view of Orlandi et al, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to clone and sequence the hybridoma of the mouse monoclonal antibodies to IL-4 which have neutralizing activity (see secondary references). A large proportion of such antibodies would have been expected to have dissociation constant of 2×10^{-10} or less. Having obtained the murine neutralizing antibodies and cloning and sequencing them, it would have been obvious to applicant methods such as those taught by Queen et al is order to develop fusion proteins which are chimeric antibodies having murine variable regions and human constant regions of humanized antibodies comprised of mouse CDR's fused to framework sequences derived from human antibodies having variable regions with high homology to the murine antibodies to be humanized. It would have been further obvious to include a pharmaceutically acceptable carrier as taught by Abrams and to include a second fusion partner as taught by Curtis et al for the purpose of increasing the desired effects. One would have been motivated to screen for a high affinity antibody with a dissociation constant equal to or less than of 2×10^{-10} in view of the teaching by Maggio that the

affinity between antigen and antibody limits the sensitivity in immunoassay procedures that use the most sensitive label-detection methods.

One of ordinary skill would have been motivated to produce the claimed antibodies and fusion proteins in view of the teaching of Coffman et al that blocking antibodies specific for IL-4 had potential for reducing IgE responses associated with certain human immune disorders together with the recognized advantages of humanized antibodies for human therapy as characterized by Co et al. One would have been motivated to produce the claimed pharmaceutical composition for use in therapy.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 5597710 and US 5705154 and US 5770403.

Claim 18 is free from the art of record because the prior art does not enable the use of a monoclonal antibody to treat IgE related disorders.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesdays and Thursdays from 5:30am to 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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sjh